## REMARKS

### STATUS OF THE CLAIMS

Claims 1-2 and 4-21 were pending in this application. Claims 1, 11, and 15 have been amended, claims 16-20 have been canceled, and claims 28-38 have been added. Following entry of the amendments, claims 1, 2, 4-15, 21, and 28-38 will be pending and at issue.

### SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claims 1 and 11 have been amended to recite "a region within" or "an active site within" to more clearly define Applicant's invention as a compound that hybridizes to a region within nucleobases 391-1639 of SEQ ID NO:3. This amendment merely corrects a grammatical error since, as the Examiner correctly pointed out, a compound 8-50 nucleobases in length could not hybridize with nucleobases 391 through 1639 of SEQ ID NO:3, but rather would hybridize to a region within nucleobases 391-1639 of SEQ ID NO:3. Support for this amendment is found throughout the specification as filed, e.g., Table 1 on pages 81-82, disclosing antisense oligonucleotides that hybridize to regions within nucleobases 391-1639 of SEQ ID NO:3.

Claim 15 has been amended to insert the language "in cell culture" and delete the language "or tissues." Support for this amendment is found throughout the specification as filed, e.g., beginning on page 70, "Example 9 Cell culture and oligonucleotide treatment."

New claim 28 is merely claim 22 rewritten to a) refer only to the elected subject matter (SEQ ID NO:58); b) be in an independent form and c) include all the limitations of the base and intervening claims (claims 1 and 2). New claims 29-38 depend on new claim 28, and mirror original claims dependent on claim 1. Applicant has added these new claims in the event that Applicant successfully overcomes the Examiner's 102/103 rejection citing Xiao et al and finds the elected subject matter free of the prior art.

The amendments to the claims therefore add no new matter and entry is respectfully requested.

**RESTRICTION REQUIREMENT**

In the Final Office Action dated 06/14/04, the Examiner acknowledged Applicant's election of SEQ ID NO:58 of claim 28. Applicant assumes Examiner meant to acknowledge Applicant's election of SEQ ID NO:58 of claim 21.

The Examiner then stated that "Claim 28 as drawn to SEQ ID NOS:41-50, 52-54, 56-61, 63-67, and 69 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention, there being no allowable generic or linking claim." Applicant assumes the Examiner was referring to claim 21, and requests clarification, since the range recited included the elected subject matter of SEQ ID NO:58.

**REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

**Claims 1, 2, 4-20 and 21** (referred to as claim 28 in the Office Action) were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite "because no compound exists that could specifically hybridize with nucleotides 391 through 1639 while simultaneously being no longer than 50 nucleotides long, because such a nucleotide must necessarily be at least 1248 nucleotides long."

Applicant has amended independent claim 1 to recite "a region within" and independent claim 11 to recite "an active site within." Claims 2, 4-9, 12-15, and 21 ultimately depend on claims 1 or 11. Claims 16-20 have been canceled. Accordingly, the pending claims are not indefinite and Applicant requests withdrawal of this rejection.

**REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

**Claims 15-20** were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner stated that "the specification ... does not reasonably provide enablement for antisense-mediated inhibition of interleukin-8 expression in vivo, or for method of treating diseases associated with its expression in vivo."

Applicant notes that the Examiner directed Applicant's attention to "cancerwebs online medical dictionary (attached)" but a copy of this document was not included in the office action, nor included in the Notice of References cited, nor can it be easily located on PAIR images.

However, a definition of "in vivo" was found at http://cancerweb.ncl.ac.uk/ and Applicant assumes this is the document used by the Examiner.

Applicant respectfully disagrees with the Examiner's rejection for reasons of record. However, without agreeing with the Examiner's arguments but rather to further prosecution, Applicant has canceled claims 16-20 and amended claim 15 to remove the language "or tissues" and add the language "cells in cell culture." Applicant reserves the right to pursue any cancelled subject matter in, e.g., a continuation application.

As the Examiner has admitted, the specification is enabled for antisense-mediated inhibition of interleukin-8 expression in vitro. Applicant requests withdrawal of this rejection as drawn to the amended claims.

**REJECTIONS UNDER 35 U.S.C. § 102/103**

**Claims 1-2 and 11** were rejected under 35 U.S.C. § 102(b) and 103(a) as allegedly anticipated and/or obvious by Blaser et al. (U.S. Patent Number 5,527,678). The Examiner stated that "SEQ ID NO:8 of Blaser et al possesses 100% identity with residues 358-392 of SEQ ID NO:3 of the instant specification and would thus specifically hybridize with nucleotides 391 and 392 of il-8 of SEQ ID NO:3." Applicant assumes that the Examiner meant to use the term "complementarity" instead of "identity." Applicant respectfully disagrees with the rejection.

First, Applicant respectfully rebuts the Examiner's prima facie case, providing evidence showing that a compound that is complementary to a target does not necessarily possess the characteristics of the claimed invention, e.g., hybridize to and inhibit expression of the target. In addition, Applicant points out the prior art compound is not complementary to a region within nucleobases 391-1639 of SEQ ID NO:3 of the instant application.

**A. The prior art compound does not necessarily hybridize to and inhibit the expression of the target.**

Applicant believes that, in rejecting the claims under 35 U.S.C. 102(b) and 103 (a), a *prima facie* case has been established by the Examiner that can be rebutted by evidence showing

that the prior art product does not necessarily possess the characteristic of the claimed product. See, for example, MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). ***Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.***

Applicant points out that an oligonucleotide that is complementary to a target sequence does not necessarily inhibit expression of the target sequence. As evidence, Applicant directs the Examiner's attention to Table 1 on pages 81-83 of the instant application. At least seven (7) of the antisense oligonucleotides (SEQ ID NOS:13, 22, 55, 62, 68, 74, and 81) are 100% complementary to the target sequence but do not have the function of inhibiting expression of the target sequence. This data provides evidence that an antisense oligonucleotide with 100% complementarity to a target sequence does not necessarily have the property of inhibiting expression of the target sequence, demonstrating that the basis for believing that the products of the applicant and the prior art are the same is not a sound basis, e.g., 100% complementarity does not necessarily mean hybridization to and inhibition of expression.

Therefore, even if the prior art product disclosed by Blaser et al was complementary to the target of the claimed invention (and Applicant shows below that it is not), it would not necessarily possess the characteristics of the claimed invention, e.g., the prior art compound does not necessarily hybridize to and inhibit expression of the target.

Applicant reminds the Examiner that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re*

*Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981); *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

**B. The prior art compound is not complementary to the claimed target.**

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Claims 1 and 11 recite a compound that hybridizes to a region within nucleobases 391-1639 of SEQ ID NO:3 of the instant application. Blaser et al does not disclose any such compounds. The compound cited by the Examiner, SEQ ID NO:8 of Blaser et al, is 25 nucleobases long, and is complementary to nucleobases 358 through 382 (not 392) of SEQ ID NO:3 of the instant application. Therefore, the compound of Blaser et al does not have complementarity to a region within nucleobases 391-1639 of SEQ ID NO:3 of the instant application, and could not hybridize to and inhibit the expression of the target. The reference thus does not disclose all the limitation of the claimed invention.

Withdrawal of this rejection is respectfully requested.

**REJECTIONS UNDER 35 U.S.C. § 102**

**Claims 1, 2, 4, 5, 8, 9, and 11-15** were rejected under 35 U.S.C. § 102(a) as allegedly unpatentable over Nyce, J (WO 99/13886). The Examiner stated that "SEQ ID NO:1292 of Nyce et al, disclosed on page 55 at lines 37-60 indeed hybridizes to applicant claimed target region of SEQ ID NO:3, namely at nucleobases 693-711, with 100% complementarity." Applicant assumes the Examiner was referring to Fragment 1292, SEQ ID NO:1302, disclosed in Nyce et al at page 55, line 50; SEQ ID NO:1302 is 100% complementary to nucleobases 693-711 of SEQ ID NO:3 of the instant application.

Applicant respectfully disagrees. Although Nyce et al discloses SEQ ID NO:1302 and includes general disclosure about the use of antisense oligonucleotides targeted to IL-8, nowhere does Nyce et al provide data showing that a compound comprising SEQ ID NO:1302 hybridizes to the target or inhibits the expression of the target. Indeed, nowhere does Nyce et al disclose antisense inhibition of IL-8 using any oligonucleotide. Therefore, the compound disclosed in

Nyce et al does not include each and every element of the claims, and does not anticipate the claims.

Withdrawal of this rejection is respectfully requested.

**REJECTIONS UNDER 35 U.S.C. § 103**

**Claims 1, 2, 4-10, and 12-15** were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Nyce *et al.* in view of Taylor *et al.*, and Baracchini *et al.* Applicant traverses this ground of rejection.

Three requirements must be met for a prima facie case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the references or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully disagrees with the Examiner for the reasons of record and incorporates herein the earlier made arguments. In summary, the cited prior art references do not teach all of the elements of the claims, e.g., the combination does not teach a region within nucleobases 391-1639 of SEQ ID NO:3. In addition, the cited art does not teach or provide a motivation to combine the teachings but instead provides, at most, a generalized scientific goal that cannot substitute for the particularity needed to establish a *prima facie* case of obviousness; the Examiner has not met the required specificity to establish a motivation to combine the references.

In addition to earlier made arguments, Applicant submits that combination of cited references fails to provide a reasonable expectation of success because the combination of cited references fails to provide direction as to which of many possible choices of Il-8 antisense molecules targeted to nucleobases 391-1639 of SEQ ID NO:3 is likely to be successful. As such,

the cited combination at best makes the claimed invention "obvious to try." It does not render it obvious. See *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Nyce provides no guidance on designing or selecting antisense oligonucleotides targeted to IL-8; at most Nyce provides a very generalized goal to do so and discloses a single, complementary sequence with unknown hybridization and/or inhibition activity. Baracchini and Taylor do not remedy this deficiency. There is nothing in the approaches to designing antisense oligonucleotides used by Baracchini nor in the sequences of the specific antisense molecules found by Baracchini that could provide direction as to the successful selection of antisense molecules that would specifically hybridize with and inhibit expression of a IL-8 nucleic acid molecule, given the completely unrelated sequences of nucleic acids encoding IL-8 on the one hand and those encoding MRP (as disclosed in Baracchini et al) on the other. Taylor provides a generalized teaching regarding antisense technology; nowhere does Taylor et al provide guidance as to how to design antisense oligonucleotides, much less how to design antisense oligonucleotides targeted to IL-8.

In the Final Office Action dated June 14, 2004, the Examiner stated "Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find on that inhibits its target 66-95%." Applicant respectfully points that this is not an example of Taylor providing an expectation of success. The complete quote from Taylor is a follows:

> The best target sites are still determined empirically, although improvements in the potency of ONs and in the algorithms used for predicting accessible sites on the target mRNA have drastically reduced the number of oligonucleotides that must be screened to fine one that is effective. Previous recommendations required the screening of 30-60 ONs per gene. Using high affinity chimeric oligomers and a bioinformatic program to select accessible sites, Woolf and coworkers have found that screening 3-6 oligomers per target is sufficient to find one that inhibits the gene with 66-95% efficiency (Sequitur, Natick, MA, USA) (unpublished data) ...

Clearly Taylor teaches that one of skill cannot predict specific active sequences without experimentation. One of skill in the art would conclude that Taylor does not teach how to design or select an oligonucleotide with antisense activity to any target (much less targeted to an IL-8),

but rather Taylor discloses that Sequitar has designed and/or or selected chimeric oligonucleotides (with antisense activity) of unknown sequences targeted to an unknown target (e.g., not to any target), using unpublished data, e.g., using methods that are not publicly known.

Accordingly, a *prima facie* case of obviousness has not been presented and withdrawal of this ground of rejection of the claims is respectfully requested.

**REJECTIONS UNDER 35 U.S.C. § 102/103: XIAO ET AL**

**Claims 1-2 and 11** were rejected under 35 U.S.C. 102(b) and 103 (a) as allegedly anticipated and/or obvious by Xiao et al. (U.S. Patent Application 220020146407). The Examiner stated that "SEQ ID NO:31 of Xiao et al possesses 100% identity with SEQ ID NO:58 of the instant specification and would thus specifically hybridize with human interleukin-8." In response, Applicant submits a declaration under 37 CFR 1.131 that proves invention of the claimed subject matter by Applicant prior to the effective date (e.g., prior to June 20, 2001) of Xiao et al. Therefore, Xiao et al is not available as prior art and withdrawal of this rejection is respectfully requested.

**CONCLUSION**

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
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